Exhibit IND3

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA – WESTERN DIVISION

NEUROGRAFIX, a California corporation; WASHINGTON RESEARCH FOUNDATION, a not-for-profit Washington corporation, Plaintiffs, vs. SIEMENS MEDICAL SOLUTIONS USA, INC., a Delaware corporation; and SIEMENS AKTIENGESELLSCHAFT, a German corporation, Defendants.	Case No. 10-CV-1990 MRP (RZx) [Assigned to The Honorable Mariana R. Pfaelzer] **REBUTTAL EXPERT REPORT OF DR. R. NICK BRYAN**
SIEMENS MEDICAL SOLUTIONS USA, INC., Counterclaimant, vs. NEUROGRAFIX, and WASHINGTON RESEARCH FOUNDATION Counterdefendants.	

REBUTTAL EXPERT REPORT OF DR. R. NICK BRYAN

I. Introduction

1. In this Report, I respond to the July 21, 2011 Expert Report submitted July 22, 2011 by Dr. Brant-Zawadzki ("Brant-Zawadzki Report"), and provide my opinions and conclusions regarding the claim phrases "a conspicuity of the nerve that is at least 1.1 times that of the non-neural tissue" (as used or incorporated into claims 1 through 17) and "a conspicuity of the nerve that is at least 1.1 times that of any adjacent non-neural tissue" (as used or incorporated into claims 18 through 35) in the claims of U.S. Patent No. 5,560,360 ("the '360 patent"), and if called upon to testify, intend to testify to the opinions disclosed herein and in my July 22, 2011 Expert Report Concerning the Term "Conspicuity" ("Bryan Opening Report").

2. This report reflects conclusions that I have formed through my independent evaluation and analysis. If called upon to testify in this matter, I anticipate that my testimony will concern the matters addressed in this and my Opening Report, the attachments to the report, and the materials I relied upon in developing my opinions, as well as any background information concerning the technology areas at issue and my own education and experience in those areas.

3. This report is based on my analysis to date, and sets forth my opinions about certain claims, and particularly certain phrases used in the claims, of the '360 patent. I reserve the right to respond to any further opinions Plaintiffs or Dr. Brant-Zawadzki offer. I also reserve the right to supplement my opinions if Plaintiffs change their proposed claim constructions, or upon the discovery or production of additional information. I also reserve the right to supplement my opinions in the event the Court modifies or supplements its claim construction.

4. As explained herein, I disagree with Dr. Brant-Zawadzki's conclusion that "average radiologists would have no problem determining conspicuity relevant to the claims of

the '360 patent in a consistent and repeatable manner and therefore be able to determine whether the claims of the '360 Patent are being practiced or not." Brant-Zawadzki Rep. ¶ 2.

5. Dr. Brant-Zawadzki's Report states that it addresses "how to select the appropriate regions of interest in [the nerve and background] to determine conspicuity according to the teachings of the '360 patent." Brant-Zawadzki Rep. ¶ 2. But, based on my review, neither the '360 patent nor Dr. Brant-Zawadzki's report adequately explains to one skilled in the art or gives examples of how to select the appropriate region of interest ("ROI") to determine the conspicuity calculation as required by the claims of the '360 patent. Based on the literature and my own experience, there is no standard way of selecting an ROI that a person of ordinary skill in the art would apply in the context of the '360 patent, and the calculated conspicuity will vary (often substantially, as shown in my Opening Report) depending on how a person chooses an ROI. As demonstrated in my Opening Report and as discussed further herein, persons of ordinary skill in the art could (and usually would) select different ROIs for the conspicuity calculation and, based only on the differences in ROI selection, could reach different conclusions as to whether a particular nerve in an image meets the conspicuity of 1.1 requirement. It is therefore my opinion one of ordinary skill in the art would not be able to determine whether claims 1-35 of the '360 patent are being practiced.

II. Background and Qualifications

6. My background and qualifications are set forth in the Bryan Opening Report, including Exhibit A thereto, which are incorporated herein by reference as if fully set forth herein.

III. Materials Considered

7. I have reviewed the Brant-Zawadzki Report, as well as the material cited and discussed therein.

8. In addition, the opinions expressed in this Report come from my review and consideration of the material cited and discussed throughout this report, as well as the material listed in **Exhibit 1** attached hereto and Exhibit B of my Opening Report. I have also considered my experience in the MRI, neuroradiology, and radiology fields.

9. If asked to testify, I may rely on any or all of these materials, including those referenced in this report as examples, as well as other materials that I may prepare to illustrate the bases of my opinion, including demonstrative exhibits, summary exhibits, testimonial aids, animations, and the like in support of my testimony. The documents and material I specifically reference in this report are exemplary and are intended to aid understanding.

IV. Level of Ordinary Skill in the Art

10. I understand that Plaintiffs contend that a person having ordinary skill in the art for the '360 patent is a medical doctor with an M.D., three years of residency and a 1 year fellowship in neuroradiology or musculoskeletal radiology and at least 2 years experience in neuroradiology or musculoskeletal radiology, or equivalent education and experience in neuroradiology or musculoskeletal radiology. Brant-Zawadzki Rep. ¶ 12. In addition, I understand that Plaintiffs contend that a person having ordinary skill in the art will also have substantial experience (*e.g.*, 2 years) designing or studying MRI machines. *Id.*

11. For the purposes of this report and reaching the conclusions herein, and unless stated otherwise, I have applied Plaintiffs' definition of the level of ordinary skill in the art at the time of the invention, as explained in my Opening Report. *See* Bryan Opening Rep. ¶¶ 10-12. My opinions in this report about the variability in ROI selection and resulting conspicuity

calculations would not change under a reasonable but different definition of the person of ordinary skill in the art. For instance, my conclusions would be the same if the appropriate level of ordinary skill in the art was found to be the level of skill proposed by Dr. Michael Moseley, namely that a person of ordinary skill in the art is someone who has worked, practiced, or conducted research in the field of magnetic resonance imaging for at least one year, and also who either has a Medical Degree and residency in radiology or who has a PhD in physical science or engineering.

12. I note, however, my opinion is that Plaintiffs' definition describes a radiologist or neuroradiologist with superior skill, not one with ordinary skill. For example, the average radiologist or even neuroradiologist typically only has robust knowledge of a select number of larger and commonly studied nerves. This would not include many of the peripheral, autonomic, or cranial nerves 3 through 12 that are within the scope of claims 1 through 35 in the patent (*i.e.*, as the Court has interpreted that phrase, nerves "listed in Taber's Cyclopedic Medical Dictionary (17th ed. 1993) on pages 182, 463 (excluding cranial nerves 1 and 2), 1290, and 1291 and/or that is otherwise not part of the central nervous system"). There are more than a hundred nerves listed as peripheral, autonomic, or cranial nerves in Taber's, most of which are only a few millimeters in size, and of more variable location and appearance than the larger nerves. And as the Court's claim construction acknowledges, the nerves actually listed in Taber's are just the relatively large, named nerves in the set of nerves recited in claims 1 through 35 of the patent. The average radiologist would have great difficulty finding many these nerves under the best of circumstances.

V. "Conspicuity" To a Person of Ordinary Skill

13. Dr. Brant-Zawadzki's report adopts Plaintiffs' position that "conspicuity of 1.1," for purposes of the '360 patent, should be calculated as the mean intensity of nerve tissue in

some ROI divided by the mean intensity of non-neural tissue in a different ROI (which I refer to as $\mathbf{S_n/S_b}$, where the subscript "**n**" refers to nerve tissue and "**b**" refers to some background tissue). *See, e.g.*, Bryan Opening Rep. ¶ 14; Brant-Zawadzki Rep. ¶ 18 ("selecting a region of interest in the nerve and a region of interest in the background tissue, and taking the ratio of the average signal intensities for the two regions of interest"); *see also* Filler Rebuttal Rep. ¶¶ 32, 38. Dr. Brant-Zawadzki's report also says that "the concept of conspicuity is well known within the radiology field." Brant-Zawadzki Rep. ¶ 16; *see also id.* ¶ 25.

14. To the extent that Dr. Brant-Zawadzki's report suggests $\mathbf{S_n/S_b}$ is the standard, industry-recognized method for all conspicuity measurements or that one of ordinary skill in the art would know to use this particular equation, from amongst the many possible ways, for determining conspicuity in the claims, I disagree.

15. First, having knowledge about the general "concept of conspicuity" does not mean that a person—one of ordinary skill, extraordinary skill, or less than ordinary skill—would in usual practice use this method for calculating conspicuity proposed by Plaintiffs. Performing the steps proposed by Plaintiffs to determine a numerical conspicuity value for a peripheral nerve is not a typical clinical task, and is not a standardized task that one would perform even in a research setting.

16. Moreover, while I have accepted Plaintiffs' proposed equation ($\mathbf{S_n/S_b}$) for the purposes of my analysis, this is a not the standard method of analyzing conspicuity, nor is there a standard or accepted method, as I explained in my Opening Report. *See* Bryan Opening Rep. ¶¶ 15-17. Dr. Tsuruda, one of the co-inventors of the '360 patent, also agrees that there is no standard definition or formula for conspicuity. 2/25/11 Tsuruda Dep. Tr. 84:8-14. Dr. Moseley also agrees that there are many different ways of determining "conspicuity" or contrast. 2/8/11

Moseley Dep. Tr. 25:11-21 ("There is almost an infinite number of ways to calculate conspicuity."); 27:19-29:5; 43:10-15 (ratio of two signal intensities is "one of hundreds of ways").

17. The literature relied upon and considered by Dr. Brant-Zawadzki also supports that there are many different ways for determining "conspicuity" and no standard definition. For example, conspicuity is often understood to account for the complexity of the shape of a structure of interest and its surroundings. *See* G. Revesz et al., *The Influence of Structured Noise on the Detection of Radiologic Abnormalities*, 9 Investigative Radiology 479, 482-84 (Nov./Dec. 1974) ("Revesz") ("the conspicuousness of a lesion depends directly on its contrast and inversely on a measure that can be loosely called the complexity of the surrounding structures.").

18. Further, $\mathbf{S_n/S_b}$ does not take into account noise, but it is very important to properly account for, and attempt to reduce the affect of, noise in any image analysis, because noise obscures the true image signal, as explained in my Opening Report. *See* Bryan Opening Rep. ¶¶ 24-27. Dr. Brant-Zawadzki's report acknowledges that noise will affect the signal intensity for any structure in an image. *See* Brant-Zawadzki Rep. ¶ 43 ("These errant voxels can occur as a result of many causes including noise in the data . . ."). The literature relied upon and considered by Dr. Brant-Zawadzki explains the importance of taking into account noise when dealing with the concept of conspicuity. *See, e.g.*, Revesz at 480 ("An image-processing problem can be conceptualized as one of enhancing some signal or eliminating some type of noise. Similarly, the detection of an abnormality can be considered a problem of separating a signal from noise."); *see also* E. Vokurka et al., *Improved High Resolution MR Imaging for Surface Coils Using Automated Intensity Non-Uniformity Correction: Feasibility Study in the Orbit*, 14 J. Magnetic Resonance Imaging, 540, 541 (2001) ("Vokurka") ("The signal-to-noise

ratio of an image is an important index of image quality."); G.J. Barker, *Technical Issues for the Study of the Optic Nerve with MRI*, 172 J. Neurological Sci. S13, S14 (2000) ("Barker"); D. Bonekamp et al., *Diffusion Tensor Imaging in Children and Adolescents: Reproducibility, Hemispheric, and Age-Related Differences*, NIH Author Manuscript (34 Neuroimage 733), at 7 (2007) ("Barker"); H.M. Bonel et al., *Carpel Tunnel Syndrome: Assessment by Turbo Spin Echo, Spin Echo, and Magnetization Transfer Imaging Applied in a Low-Field MR System*, 25(1) J. Computer Assisted Tomography 137, 138-39 (2001) ("Bonel"); V. Juras et al., *Regression Error Estimation Significantly Improves the Region-of-Interest Statistics of Noisy MR Images*, 37 Med. Phys. 2813, 2814 (2010) ("Juras").

19. Dr. Tsuruda also agrees that noise should be taken into account in image analysis or calculations, because of its potential to obscure image data, thus making the true structures difficult or impossible to delineate. *See* 2/25/11 Tsuruda Dep. Tr. 181:20-24 ("Typically, as I mentioned, I always put a noise characterization in there because sometimes when you have a lot of noise in the image the data is not as reliable, instead of going to just straight signal intensity.").

VI. Nerves Are Not the Brightest, Most Intense Tissue in Images Plaintiffs Say Were Created Using the Methods Claimed in the '360 Patent

20. Dr. Brant-Zawadzki's report suggests that one of ordinary skill will be able to determine whether the "conspicuity" limitation is met because, according to his report, the '360 patent produces images of "nerves [that] are brighter than any other structure in the image," "the increased nerve conspicuity is on the order of ten-fold," and the patented method "results in the nerve signal being more intense than any other tissue." Brant-Zawadzki Rep. ¶¶ 21, 26; *see also id.* ¶ 39.

21. I disagree with those statements in Dr. Brant-Zawadzki's report. Nerves in the images that Plaintiffs say were made using the patented method, *see* Filler Rebuttal Rep. ¶ 48; Plaintiffs' Claim Construction Reply Br. 8 ("the image of a peripheral nerve using the method disclosed in the '360 patent used by Dr. Filler consistently has conspicuity of greater than 1.1 times"), are not brighter (or more intense) than all other structures or tissues in the images. *See, e.g.*, Bryan Opening Rep. ¶¶ 44(a), 55, Ex. C, Fig. 3 & Table 3. Likewise, the nerve conspicuity in those images is not on the order of "ten-fold." *Id.* Rather, there are many instances in those images in which non-neural tissue (rather than the nerve tissue) is the brightest, most intense structure. *Id.*

22. In Figure 1 of Exhibit C of my Opening Report (which is the same MR image used in Exhibit A, Figure 4 of the Filler Rebuttal Report), several non-neural tissues, for example those identified by ROIs 2, 3, 4, and 9, are the brightest, most intense tissue. *See id.* Ex. C, Fig. 1 & Table 1. Also, in Figure 3 of Exhibit C of my Opening Report (which is the same MR image used in Exhibit A, Figure 3 of the Filler Rebuttal Report), several non-neural tissues, for example those identified by ROIs 2 and 14, are the brightest, most intense tissue. *See id.* Ex. C, Fig. 3 & Table 3.

23. In fact, as shown in **Exhibit 2** attached to this report (using the same images I used in my Opening Report and that Dr. Filler used in his Rebuttal Report), several of the images Plaintiffs say were made using the patented method result in the nerve tissue not even having signal intensity values within the brightest 50% (approximately) of the pixel signal intensities in the image. *See* **Ex. 2**, Figs. 1-13.[1] That is, the signal intensities of the nerves are less than 50% of the maximum signal intensity of other tissues found in the image. For example, for the image

[1] These images were created using MIPAV, version 4.3.0 software.

corresponding to Ex_C_3.dcm DICOM data (corresponding to Exhibit A, Figure 8 of the Filler Rebuttal Report), no neural tissue exhibits signal intensity values within the brightest 50% (approximately) of the signal intensities in the image. *See* **Ex. 2**, Fig. 12-13.

24. Similarly, for the image corresponding to Ex_C_5.dcm DICOM data (corresponding to Exhibit A, Figure 3 of the Filler Rebuttal Report), no neural tissue exhibits signal intensity values within the brightest 50% (approximately) of the pixel signal intensities in the image. *See* **Ex. 2**, Fig. 2-5. While a very few neural tissue pixels fall within the brightest 60% of the signal intensities, *see* **Ex. 2**, Fig. 6, nerves are not reasonably observed until the brightest 70% of pixel signal intensities are included. *See id.* Fig. 7. However, as is evident from Figures 6 and 7, the brightest 60-70% of pixel signal intensities also contains a large amount of non-neural tissue. *Id*; *see also* Figs. 8-10 (showing that, for the image corresponding to Ex_C_2.dcm, no neural tissue is visible within the brightest 20% of pixel signal intensities).

25. Accordingly, using the brightest pixel signal intensities in the image does not provide a threshold to help in selecting which pixels or areas to include for the conspicuity calculation. Even if one of ordinary skill in the art were to use the brightest 50% of the pixel signal intensities (far from the brightest or most intense) as a threshold for determining which pixels are neural tissue and which pixels are not, such an approach would not isolate neural tissue so that it could be measured or selected with an ROI for the conspicuity calculation.

VII. One of Ordinary Skill Would Not Know the Bounds of the "Conspicuity" Term

26. Dr. Brant-Zawadzki's report says that "a person having ordinary skill in the art would understand the bounds of the 'conspicuity' term because the identification and selection of a nerve and surrounding non-neural tissue and of regions of interest are commonplace and well-known tasks for radiologists." Brant-Zawadzki ¶ 24. As discussed in my Opening Report and

further herein, I disagree. Even if one of ordinary skill in the art was generally able to identify nerve and non-neural tissue, and even if selecting regions of interest to calculate the average intensity of nerves and surrounding tissue was a common task for a person of ordinary skill in the art, those conclusions do not mean that one of ordinary skill in the art would reliably or consistently choose the same or even similar regions of interest, or that different regions of interest will not affect the conclusions as to whether an image meets the "conspicuity of 1.1" phrase. Each radiologist or person of ordinary skill in the art could, and often would, choose different regions of interest and therefore reach different conclusions as to whether an image shows the required 1.1 conspicuity for nerves.

A. Identifying a Nerve and Non-Neural Tissue and Selecting ROIs for that Tissue

27. I note that an average radiologist or even neuroradiologist is trained to identify only a small number of nerves, and usually only those that are relatively large. But identifying the smaller nerves and especially their boundaries (including many of the nerves recited in the claims), for any radiologist or neuroradiologist, becomes more difficult or even impossible, as Dr. Brant-Zawadzki recognizes. *See* Brant-Zawadzki ¶ 39 ("The techniques above are only necessary if the person of ordinary skill is unsure if the conspicuous structure is a nerve, such as may happen for the smaller peripheral nerves."). Drawing ROIs within those nerves is therefore even more difficult, considering that some of those nerves are less than 1 mm in size.

28. While I do not disagree that one of ordinary skill (under Plaintiffs' definition of the level of ordinary skill) might be able to identify the general location of some of the nerves recited in the claims, that by itself does not mean that one of ordinary skill would understand the bounds of the claimed "conspicuity of 1.1." An observer cannot accurately distinguish between tissue boundaries, or reliably and consistently select ROIs for both neural and non-neural tissue,

nor can the observer tell which pixels (*i.e.*, size, shape, and position) to include in the ROIs. As discussed in my Opening Expert Report, *see* Bryan Opening Report ¶¶ 29-40, and below, selecting the ROIs for both the neural and non-neural tissue is subjective and significantly affects the calculation of $\mathbf{S_n/S_b}$.

29. Indeed, this is especially true considering that Plaintiffs' proposed definition ($\mathbf{S_n/S_b}$) does not take into account noise, yet noise obscures the true image signal, making the selection and placement of an accurate ROI even more difficult, imprecise, and prone to operator subjectivity, which Dr. Brant-Zawadzki acknowledges. *See* Brant-Zawadzki Rep. ¶ 43 ("These errant voxels can occur as a result of many causes including noise in the data . . ."). The literature relied upon and considered by Dr. Brant-Zawadzki also recognizes that noise obscures the true image signal, making it harder to distinguish between structures in the image. *See infra* ¶ 18.

30. Dr. Brant-Zawadzki's report says that a person of ordinary skill will use other techniques and image-sets to identify a nerve. Brant-Zawadzki Rep. ¶ 35. Even assuming that a person of ordinary skill can use other images to determine whether a structure is a nerve (if they cannot do so based on one image), selecting ROIs for calculating conspicuity as proposed by Plaintiffs occurs on a single image, as demonstrated by Dr. Filler's image analysis in his Rebuttal Report. *See* Filler Rebuttal Rep. Ex. A. Thus, although other image sets and imaging techniques might assist a person of skill in the art in identifying the general nerve structure and/or location within the patient, the ROI for the conspicuity calculation proposed by Plaintiffs ultimately must be drawn in a single image.

31. Like his opinion regarding identifying the nerve, with regard to non-neural tissue Dr. Brant-Zawadzki's report also says that "[d]istinguishing one type of tissue from another is

part of the anatomic functions for a radiologist's every day work." Brant-Zawadzki Rep. ¶ 38. While one of ordinary skill in the art may be able to identify the general location of non-neural tissue, that does not mean that the observer can accurately distinguish between tissue boundaries or that ROIs can be reliably or consistently selected for both neural and non-neural tissue, nor does it tell the observer which pixels (*i.e.*, size, shape, and position) to include. Thus, as discussed in my Opening Expert Report, *see* Bryan Opening Report ¶¶ 29-40, and below, *see* ¶¶ 32-44, selecting the ROIs for both the neural and non-neural tissue is subjective, and Dr. Brant-Zawadzki's report does not show otherwise.

B. There is No Industry-Accepted Standard for Selecting ROIs, Especially for the Nerves Recited in Claims 1 Through 35

32. Dr. Brant-Zawadzki's report says that one of ordinary skill in the art would know how to calculate the "conspicuity" in claims 1-35 because "a person of ordinary skill will also know what portion of the region of interest to choose" and that he or she "knows to select a representative portion of the region." *See* Brant-Zawadzki Rep. ¶¶ 41-43; *see also id.* ¶ 38. His report also says that an average radiologist would know to "select the surrounding tissue with the strongest signal strength (brightest) to determine whether the conspicuity" limitation is met. *Id.* ¶ 38; *see also id.* ¶¶ 44, 48. For the reasons discussed herein and in my Opening Expert Report, I disagree.

33. I disagree that one of ordinary skill in the art would consistently select the same "representative" portion of the nerve or surrounding tissue based on the teachings in the '360 patent or based on their knowledge as a person of skill in the art. There is no industry-accepted standard for which pixels are "representative" of a particular tissue, nor is there an industry-accepted standard for selecting a "representative" portion of a nerve or surrounding tissue. And nothing in the '360 patent teaches how to draw an ROI that includes a "representative" portion of

the tissue. As explained in my Opening Report, the average signal intensity of the nerve and non-neural tissue will vary greatly depending on not only the size and shape of a particular ROI, but also its placement within the tissue, which consequently causes the conspicuity measurement to vary greatly as well. *See* Bryan Opening Rep. ¶¶ 50-58.

34. In addition, as I explained in my Opening Expert Report, there is no recognized standard for selecting an ROI and, as a result, when an application calls for evaluating image quality or characteristics based on an ROI, the precise parameters and protocol for selecting the ROI are specified. *See* Bryan Opening Rep. ¶¶ 30-35.

35. The articles relied upon by Dr. Brant-Zawadzki do not show otherwise. Although Vokurka shows selecting an ROI for a particular measurement, it does not support that there is an industry-accepted standard for selecting ROIs, or a "representative" portion of a structure. Instead, consistent with my opinion, Vokurka specifies and illustrates not only the size of the ROI's used in the measurements, but also the locations (*e.g.*, the anterior and posterior globe, fat at the midpoint of the orbit, and temporalis muscle). Vokurka at 541-42.

36. Similarly, the other literature that Dr. Brant-Zawadzki relied upon and considered also supports that there is no industry-accepted standard way of selecting an ROI and, when ROIs are necessary for measurement purposes, they are specified with particularity. *See, e.g.*, S. Bisdas et al., *Reproducibility, Interrater Agreement, and Age-Related Changes of Fractional Anistropy Measures at 3T in Healthy Subjects: Effect of the Applied b-Value*, 29 Am. J. Neuroradiology 1128, at 1129 (2008) ("Bisdas"); Bonekamp at 4, 9 & Fig. 2.

37. Dr. Brant-Zawadzki's report also says that a person of ordinary skill will not "include multiple structures, or go [ ] across structure boundaries" when selecting an ROI, and would "include[ ] only the structure of interest." *See* Brant-Zawadzki Rep. ¶ 42. But at the same

time he acknowledges that precisely determining where the boundary between neural and non-neural tissue lies can be difficult as "a result of many causes including noise in the data and partial volume averaging (where the voxel is actually representative of the average signal intensity of two adjacent structures)." Brant-Zawadzki Rep. ¶ 43. Moreover, Dr. Brant-Zawadzki acknowledges that, for smaller peripheral nerves (which can be less than 1 mm), a person of ordinary skill may be unsure if the structure is in fact a nerve, *id.* at ¶ 39, which demonstrates that for those nerves (which outnumber the larger, more readily identifiable peripheral nerves) it would be extremely difficult (bordering impossible) to draw an ROI so as not to "include multiple structures, or go [ ] across structure boundaries." *Id.* ¶ 42.

38. Dr. Brant-Zawadzki's report also says that, in selecting only the structure of interest, the person of ordinary skill will also seek to exclude "errant voxels" "which they believe are not actually part of the structure," such as pixels or voxels that "can occur as a result of many causes including noise in the data and partial volume averaging." Brant-Zawadzki Rep. ¶ 43. But there is no objective way for one of ordinary skill in the art to reliably determine which pixels are errant voxels or pixels corresponding to noise or partial volume averaging. Even if a person of ordinary skill in the art attempted to exclude such "errant voxels" or pixels, doing so would rely on the observer's subjective visual determination about which voxels or pixels were part of the structure and which were not. Given the anatomic complexity of peripheral nerves, this would be even more difficult (if not impossible) for the smaller peripheral nerves (which can be less than 1 mm).

39. If the errant voxel is located within the nerve, the operator would be required to manually draw an ROI around the errant voxel(s), draw an ROI around the remaining neural tissue, and then somehow subtract the signal intensity value of the errant voxels, so that only the

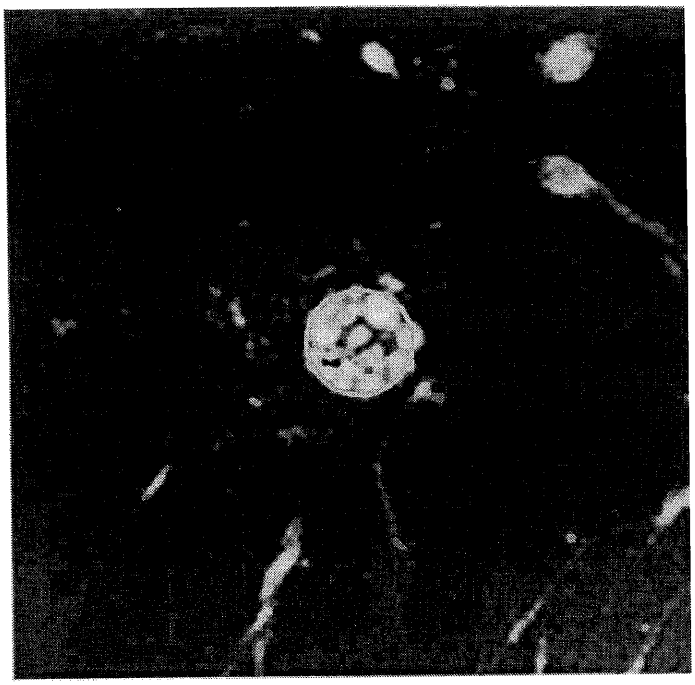
signal intensity of the tissue of interest is selected. But Dr. Brant-Zawadzki has cited no support from the '360 patent for this approach and it is not a method that one of ordinary skill would typically perform if asked to select an ROI for a nerve. And doing so would be based on the operator's subjective visual judgment about very small areas in an image.

40. Partial voxel averaging is where the voxel at the boundary of two tissues is actually representative of the average signal intensity of two adjacent structures, rather than representing the signal intensity of one structure, such as a nerve. Those of ordinary skill in the art typically are not required, nor would they be able, to perform ROI selection manually with such accuracy as to exclude single pixels that they believe are the result of partial voxel averaging.

41. Dr. Brant-Zawadzki's report also says that a person of ordinary skill in the art would "not be confused as to whether to use the whole nerve or some subsection of the nerve, because the claim says to calculate the conspicuity of the 'nerve,'" and would therefore know to take the signal intensity of the entire structure, *i.e.*, the entire nerve. Brant-Zawadzki Rep. ¶¶ 43, 45. For several reasons, I disagree that one of ordinary skill in the art would know or be able to select the entire nerve based on the teachings in the '360 patent or their knowledge as one of skill in the art. Rather, as explained in my Opening Report, neither the claims nor the '360 patent provide sufficient guidance about what "nerve" tissue to include as part of the "nerve," nor how to select an ROI within it, for purpose of the neural ROI. *See* Bryan Opening Rep. ¶ 46.

a. First, in suggesting that one should select the entire nerve or structure, Dr. Brant-Zawadzki's report says that "[i]f the structure is less uniform, such as if the fascicle pattern in a nerve is visible, the person of ordinary skill in the art will select the entire structure." *Id.* ¶ 43. This would apparently mean selecting the entire fascicle bundle, for

example as shown below with Figure 21 from the '360 patent (annotated with a red ROI). But Dr. Brant-Zawadzki's report also says to "exclude voxels which they believe are not actually part of the structure." *Id.* at 43. Whether one of ordinary skill in the art should include the dark signal in the ROI below (which could be noise, vessel, or endo/perineureum, etc.), or should instead attempt to exclude it, is a question that is not answered by the '360 patent or the knowledge of person of skill in the art.



b. Second, Dr. Brant-Zawadzki's suggestion to select the whole nerve is inconsistent with his opinion that one of ordinary skill in the art would know to select a "representative portion" of the nerve. *See, e.g.*, Brant-Zawadzki Rep. ¶ 43. It is also inconsistent with the statement in the patent that an ROI can be a single pixel. '360 patent col.14 ll.56-59.

c. Third, while Dr. Brant-Zawadzki suggests that one of ordinary skill would know to select the whole nerve, *see id.* ¶ 45, Dr. Filler selected only portions of the nerve

when performing the conspicuity calculations in his Rebuttal Report. *See* Filler Rebuttal Rep., Ex. A, Figs. 1-8.

d. Fourth, to the extent one would select the whole nerve, for images like those in Ex. C, Figure 11 of my Opening Expert Report, this would require manually tracing an ROI by precisely following the entire nerve tract. Doing so would greatly depend on the visual subjective assessment and hand-eye-coordination of the operator, and greatly increase the chance for error and the chance of including tissue that is not part of the nerve. To the extent one chooses to use a segmentation algorithm rather than manually selecting an ROI, and to the extent the '360 patent refers to "automatically" selecting ROIs, *see* '360 patent col.14 ll.59-63, however, there are many known segmentation algorithms in the art each with varying results and there is no industry standard. *See, e.g.*, L.P. Clarke et al., *MRI: Stability of Three Supervised Segmentation Techniques*, 11 Magnetic Resonance Imaging, 95, at 100 (1993) ("Clarke") ("[F]or tissues that are not well differentiated such as white and gray matter, differences in segmentation were observed particularly between the MLM and the *k*-NN and ANN technique."). Yet the '360 patent does not provide any indication as to which algorithm to use. Bryan Opening Rep. ¶ 40. And even if one of ordinary skill in the art tried to use a "segmentation algorithm," to my knowledge there is no algorithm that can reliably define the boundary of most of the nerves that are in the categories of nerves listed in the claims.

42. I note that Dr. Brant-Zawadzki also makes comparisons to selecting an ROI for an aneurysm or tumor. *See, e.g.,* Brant-Zawadzki Rep. ¶¶ 36, 37, 44. Although there is no generally-accepted standard for selecting ROIs, there are some well described and validated

ways and methods to draw ROIs specifically for tumors and aneurysms. Even using these methods, there will be variability. By contrast, to my knowledge there are no standard and validated methods specifically for drawing ROIs for peripheral nerves and therefore it is critical to define how to select an ROI here. *See* Bryan Opening Rep. ¶¶ 30-35.

43. I also disagree that Dr. Tsuruda supports Dr. Brant-Zawadzki's opinion with respect to selecting neural and non-neural ROIs. *See* Brant-Zawadzki Rep. ¶ 45. Even if Dr. Tsuruda explained that one of ordinary skill can identify nerve and non-neural tissue, as suggested in Dr. Brant-Zawadzki's report, that does not support that one can perform the conspicuity calculation of claims 1-35. As explained above, *see* ¶¶ 28-31, that does not mean that he or she can accurately distinguish between tissue boundaries to select ROIs, or know which ways, among many, to define an ROI. The portions of Dr. Tsuruda's testimony cited in the Brant-Zawadzki Report ¶ 45 do not suggest differently. In the portion of Dr. Tsuruda's testimony cited by Dr. Brant-Zawadzki, Dr. Tsuruda was referencing a method of determining conspicuity based on the visual judgment of "four or five individuals," not calculating conspicuity based on using ROIs. 2/25/11 Tsuruda Dep. Tr. at 86:3-13.

44. Consistent with what I explained in my opening report and the skill of one of ordinary skill in the art, Dr. Moseley also testified that, without any guidance, there are "any number of different ways of defining an ROI," and what to include in those ROIs depends on what you are measuring. 2/8/11 Moseley Tr. 40:24-41:8; 41:17-42:11 ("I could define the number of pixels within that region that I am interested in; right.").

C. One of Ordinary Skill in the Art Cannot Determine Whether the Claims Are Being Practiced

45. I disagree with Dr. Brant-Zawadzki's opinion that "there would likely be little variability in the identification and selection of the structures" in the MR image and therefore one of ordinary skill in the art could determine whether the claim is being practiced. *See* Brant-Zawadzki Rep. ¶ 46. Rather, as detailed in my Opening Expert Report, claims 1-35 fail to reasonably apprise those skilled in the relevant art of the patent applicant's intended scope of the invention, because the underlying method of selecting an ROI for the nerve tissue and non-neural tissue in the calculation of conspicuity in claims 1-35 is subjective, imprecise, and subject to variability, and therefore leads to significant variability in the conspicuity calculations.

46. Indeed, the articles cited by Dr. Brant-Zawadzki in ¶ 46 of his report, based on my review, do not show that there is little variability, as little as 5% according to Dr. Brant-Zawadzki, and instead support my conclusions. For example, based on my review, Clarke does not discuss inter-operator variability rates or that those rates are low, as Dr. Brant-Zawadzki's report suggests. Rather, the article evaluates the performance of three segmentation algorithm techniques, *id.* at 96 ("In this paper methods from three families of supervised pattern recognition techniques for tissue classification are compared."), and supports my conclusions that the resulting calculation will appreciably vary depending on how the ROI is selected and based on the influence of the operator. *Id.* at 101 ("The influence of the operator is very large, as can be seen in the top graphs (ROI dependence)."); 103 ("The authors found MLM to be the best classifier of the methods tested. It should be noted that in that report ***error rates of 50%*** for the 'best' classifier MLM were observed."); 105 ("showing that ANN and *k*-NN perform considerably better than MLM"). Similarly, based on my review, it is unclear which portion of the V.N. Thijs et al., *Influence of Arterial Input Function on Hypoperfusion Volumes Measured*

with Perfusion-Weighted Imaging, Stroke 94 (Jan. 2004) ("Thijs") article Dr. Brant-Zawadzki relied upon, as his report does not specify which portion of the article he is citing, and I see nothing in the article to support the proposition for which it is cited.

47. As I have explained, there is no recognized standard for selecting an ROI and, in order to account for and reduce variability, the precise parameters and protocol for selecting the ROI are specified when an application calls for evaluating image quality or characteristics based on an ROI. Indeed, the literature relied upon and considered by Dr. Brant-Zawadzki, supports my opinion that a person of skill in the art would precisely define an ROI selection protocol in order to keep measurements uniform so as to reduce variability, which would otherwise be significant and a serious problem. *See, e.g.*, Bisdas at 1129, 1132 ("Therefore, as pointed out by other researchers, the interobserver variability, which may be 3 times higher than the intraobserver variability, remains a serious problem in the interpretation of the FA maps."); Bonekamp at 5, 7-8; Clarke at 101 ("The influence of the operator is very large, as can be seen in the top graphs (ROI dependence)."); E. Jackson et al., *Accuracy and Reproducibility in Volumetric Analysis of Multiple Sclerosis Lesions*, 17 J. Computer Assisted Tomography 200, at 200, 202 (1993) ("Jackson"); Juras at 2820; A. Ozturk et al., *Regional Differences in Diffusion Tensor Imaging Measurements: Assessment of Intrarater and Interrater Variability*, 29 Am. J. Neuroradiology 1124, at 1126 (2008) ("Ozturk"). As demonstrated in this literature, it is important to precisely define not only the size and shape of the ROI being used, but also its placement within the structures being measured. *See, e.g.*, Bonekamp at 4.

48. In addition, the email from Dr. Mori, a leading MRI scientist at Johns Hopkins University, to another MRI scientist, which Dr. Brant-Zawadzki considered for his report, supports my conclusion that one should specifically define a consistent way of selecting and

placing ROIs in order to reduce variability in the results. *See* Mori Email at NEURO00036336 ("Now, going back to the two different results from the same image, all you can do is to apply the same criteria when you define a structure. When we draw ROIs to define a boundary, we should try to be consistent.").

49. Also, the portion of Dr. Moseley's testimony relied upon by Dr. Brant-Zawadzki in paragraph 47 is taken out of context and does not support the suggestion that selection of the ROIs will not have a measureable effect on the conspicuity measurement. Brant-Zawadzki Rep. ¶ 47. Dr. Moseley testified that variation would be "measureable." 2/8/11 Moseley Dep. Tr. 132:14-20. While he did state that the variability may be small, he was explaining that the variability may be small ***even when the same operator performed the same measurement twice.*** *Id.* at 132:21-133:2. Similarly, Dr. Tsuruda testified that "the region selected to measure [the] intensity makes a difference if you are trying to do some quantitative conspicuity measure." 2/25/11 Tsuruda Dep. Tr. 91:20-92:6.

50. Dr. Brant-Zawadzki further says that to "show the claims to be indefinite, [one] would have to provide evidence that the selection of ROI[s] according to standard practices by a radiologist of ordinary skill in the art would affect whether the threshold of 1.1 is met." Brant-Zawadzki Rep. ¶ 48. As demonstrated in my Opening Report, *see, e.g.*, Bryan Opening Rep. ¶¶ 46-58; Ex. C, Fig. 6 & Table 6, the selection of ROIs according to standard practices of a radiologist affects whether the 1.1 threshold is met.

51. Dr. Brant-Zawadzki also says that, when the method of the '360 patent is used, "there will be no question to a person of ordinary skill in the art whether a resulting image meets the requirements of the 'conspicuity' term because the nerve will be much greater than 1.1 times more conspicuous than surrounding tissue." Brant-Zawadzki Rep. ¶ 48. He therefore seems to

suggest that determining whether the conspicuity limitation in the '360 patent is met can be accomplished simply through visual inspection of an MR image, rather than a quantitative measurement. *See also id.* ¶ 39 (noting that the nerves "will be very conspicuous" and quantitative techniques "are only necessary if the person of ordinary skill is unsure if the conspicuous structure is a nerve"). But Plaintiffs' positions on those claims require a quantitative measurement to determine whether an image shows conspicuity of 1.1.

52. Finally, Dr. Brant-Zawadzki says there is no more specific way within the art to describe the "conspicuity" term than the method used in the claims of the '360 patent. Brant-Zawadzki Rep. ¶ 49. But as demonstrated by the literature, even in the articles relied upon and considered by Dr. Brant-Zawadzki, those of ordinary skill in the art specify precisely how to define ROIs when they are required for calculations. *See, e.g.*, *infra* ¶ 38; Bryan Opening Rep. ¶¶ 32-34 (references cited therein); Bisdas at 1129; Bonekamp at 4. For instance, Bonekamp specifies and illustrates precisely how to define the ROI, and where to place it, for the measurement being performed, as well as explains that "all raters were given a template" about how to select ROIs:

> Ellipsoid ROIs were placed along the long axis of the particular fiber tract in one slice, spaced so as to sample different regions of the tract. The size of the ellipsoid ROIs was chosen to encompass 16 pixels (from interpolated data to a 250x250 matrix), and the number of ellipsoid ROIs to be placed on one single fiber tract cross-section was predefined for each ROI on a template given to all operators (number of ellipsoid ROIs: cerebral peduncle (2), anterior limb of the internal capsule (3), posterior limb of the internal capsule (3), genu of the corpus callosum (2), superior corona radiata (5); cingulum (5)). ROIs were drawn five times by one rater (D.B.) (with evaluations separated by 1 to 3 days) to evaluate the intra-rater reproducibility of the method, and one time by four raters (D.B., L. M. N.-P., M.D., M.M.) for inter-rater reproducibility analysis. All raters were given a template (corresponding to Figure 2) and performed their evaluations independently.

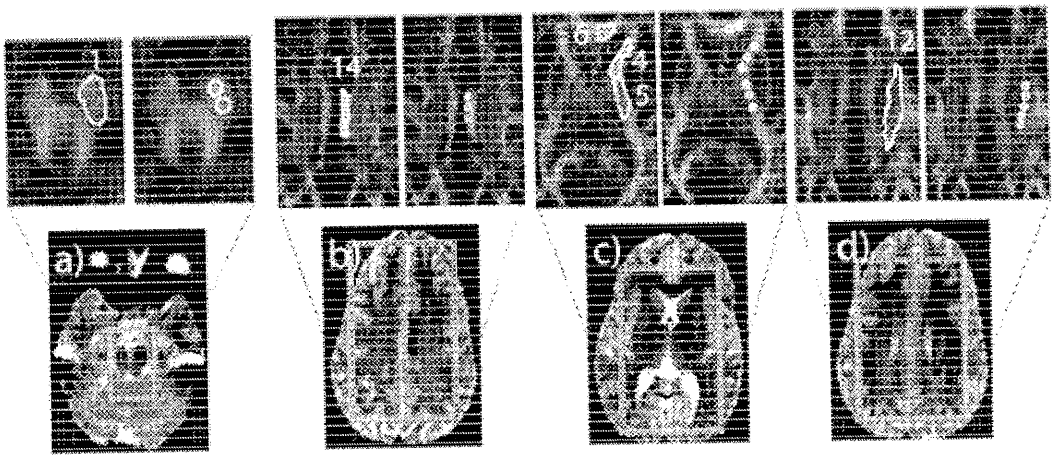


Figure 2. ROIs for reproducibility analysis

Bonekamp at 4 & Fig. 2. Thus, although the '360 patent could have explained a more objective and reliable way to determine whether the required image quality (i.e., conspicuity of 1.1) had been achieved, the patent fails to do so.

I declare (or certify, verify, or state) under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: August 8, 2011

Dr. R. Nick Bryan, M.D., PhD